Complete Summary

GUIDELINE TITLE

Diagnosis and management of basic infertility.

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Diagnosis and management of basic infertility. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2004 Jul. 47 p. [85 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Male and female infertility

GUIDELINE CATEGORY

Diagnosis
Management
Screening
Treatment

CLINICAL SPECIALTY

Endocrinology
Family Practice
Internal Medicine
Nursing
Obstetrics and Gynecology
Urology

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

- To increase the assessment of male partners during the initial infertility work-up
- To increase the rate of women who receive a basic infertility work-up before laparoscopic or surgical intervention
- To increase the rate of aggressive testing for women over 35 years of age who present with infertility
- To improve the laboratory analysis of semen samples in the infertility work-up
- To improve the rate of screening for coexisting metabolic disorders in patients with androgenic ovulatory disorders

TARGET POPULATION

Couples presenting with infertility problems

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Complete history and physical examination for both partners
2. Evaluation of female infertility factors, including ovulation dysfunction, luteal phase defect, uterine anomalies, and fallopian tube occlusion:
    - Assessment of ovulatory function by basal body temperature, serum progesterone levels, or luteal phase
    - Hormonal work-up including measurement of thyroid stimulating hormone (TSH), prolactin, follicle stimulating hormone (FSH) and luteinizing hormone, estradiol, progesterone, total serum testosterone, dehydroepiandrosterone sulfate (DHEA-S), 17 hydroxyprogesterone, fasting and 2-hour post blood glucose testing, and fasting lipid panel including total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides, if appropriate
    - Referral for hysterosalpingography
    - Laparoscopy
    - Progesterone challenge test
3. Evaluation of male infertility factors, including semen analysis

Management/Treatment

1. Clomiphene for ovulation dysfunction
2. Metformin alone or in combination with clomiphene
3. Alternative ovulation induction with gonadotropin therapy or ovarian drilling
4. In-vitro fertilization (IVF)

5. Referral to specialist
6. Patient counseling
7. Surgical treatments, such as tubal cannulation, tubal anastomosis for female
8. Empiric treatment with antibiotics and anti-inflammatories

Screening

Screening for rubella and varicella susceptibility by history of vaccination or by serology

MAJOR OUTCOMES CONSIDERED

Not stated

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

No additional description of literature search strategies is available.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Clinical Validation-Pilot Testing
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Institute Partners: System-Wide Review

The guideline draft, discussion, and measurement specification documents undergo thorough review. Written comments are solicited from clinical, measurement, and management experts from within the member medical groups during an eight-week period of "Critical Review".

Each of the Institute's participating medical groups determines its own process for distributing the guideline and obtaining feedback. Clinicians are asked to suggest modifications based on their understanding of the clinical literature coupled with their clinical expertise. Representatives from all departments involved in implementation and measurement review the guideline to determine its operational impact. Measurement specifications for selected measures are developed by the Institute for Clinical Systems Improvement (ICSI) in collaboration with participating medical groups following general implementation of the guideline. The specifications suggest approaches to operationalizing the measure.

Guideline Work Group: Second Draft

Following the completion of the "Critical Review" period, the guideline work group meets 1-2 times to review the input received. The original guideline is revised as necessary and a written response is prepared to address each of the suggestions received from medical groups. Two members of the OB/GYN Steering Committee carefully review the Critical Review input, the work group responses, and the revised draft of the guideline. They report to the entire committee their assessment of two questions: (1) Have the concerns of the medical groups been adequately addressed? (2) Are the medical groups willing and able to implement the guideline? The committee then either approves the guideline for pilot testing as submitted or negotiates changes with the work group representative present at the meeting.

Pilot Test

Medical groups introduce the guideline at pilot sites, providing training to the clinical staff and incorporating it into the organization's scheduling, computer, and other practice systems. Evaluation and assessment occur throughout the pilot test phase, which usually lasts for three months. Comments and suggestions are solicited in the same manner as used during the "Critical Review" phase.

The guideline work group meets to review the pilot sites' experiences and makes the necessary revisions to the guideline, and the OB/GYN Steering Committee reviews the revised guideline and approves it for implementation.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The recommendations for the management of infertility are presented in the form of 5 algorithms, accompanied by detailed annotations. Algorithms are provided for Initial Screening, Basic Infertility Work-Up, Evaluation of Ovulation Dysfunction, Abnormal Hysterosalpingogram, Male Infertility - Primary Care Work-Up. Clinical highlights and selected annotations (numbered to correspond with the appropriate algorithm) follow.

Class of evidence (A-D, M, R, X) ratings are defined at the end of the "Major Recommendations" field.

Clinical Highlights for Individual Clinicians

1. Provide education materials (literature, Web sites) and refer to appropriate resources. (Algorithm I, Annotation 3)
2. The basic work-up of the infertile couple should include complete history and physical, ovulation documentation, semen analysis, and hysterosalpingography. (Algorithm I, Annotation 4)
3. Be respectful of timely testing for women 35 years of age and over who present with infertility. (Algorithm II, Annotation 2)
4. Semen analysis and common interpretation of semen parameters is an essential component of the basic infertility work-up. (Algorithm II, Annotation 22)

Algorithm I: Initial Screening

2. Couple Meets Criteria for Infertility Work-Up?

   Infertility suggests factors that create an absolute inability to conceive, whereas subfertility describes factors due to a relative inability to conceive. For the purpose of brevity, the guideline developers use the term "infertility" but assume that most fertility problems are relative in severity.

   Initiation of an infertility evaluation should be undertaken after 12 menstrual cycles or one year of unprotected intercourse, or after 6 menstrual cycles or 6 months of unprotected intercourse for women 35 years old or older. Evaluation could be considered earlier in situations with significant historical

factors that could compromise fertility, such as irregular cycles, pelvic inflammatory disease (PID), or previous infertility.

Evidence supporting this recommendation is of class: R

3. Provide Couple with Education Materials and Refer to Appropriate Resources

Many lifestyle factors can be identified in the history and physical that can affect fertility. These include but are not limited to smoking, alcohol and street drug use, caffeine use, calcium channel blocker use, excess travel limiting optimal coital timing, use of lubricants or douching with coitus, excess hot tub use, and excess exercise.

4. Infertility Work-Up

It is important to regard infertility as a two-patient disorder involving both the female and the male partners. A complete and detailed history and physical needs to be done on the couple including a thorough family history, past medical history, social and sexual history, and general health history. Any previous medical evaluations and other relevant studies should be reviewed. Refer to the National Guideline Clearinghouse (NGC) summary of the Institute for Clinical Systems Improvement (ICSI) guideline Routine Prenatal Care, "Risk Profile Screening" Annotation.

Provide preconception counseling to the couple including the need for folic acid supplementation in the female. Refer to the NGC summary of the Institute for Clinical Systems Improvement guideline Routine Prenatal Care, "Nutritional Supplements" annotation for the complete text on folic acid supplementation. Some of the couples may require special counseling, especially in dealing with the psychological implications of infertility. Exposure to excessive stress may have hypothetical concerns for infertility. These issues are not able to be documented, and the patient should be counseled about stress reduction techniques if appropriate.

Provide couple with health educational materials. Many lifestyle factors can be identified in the history and physical that can affect fertility. These include but are not limited to smoking; alcohol and street drug use; caffeine use; calcium channel blocker use; excess travel limiting optimal coital timing; use of lubricants or douching with coitus; excess hot tub use; and excess exercise. Many over-the-counter botanical preparations can have an adverse effect on infertility (e.g., ginkgo biloba may adversely affect sperm).

Evidence supporting this recommendation is of class: R

6. Immunize Against Rubella and/or Varicella

Screen for rubella and varicella susceptibility by history of vaccination or by serology. Do not give measles, mumps, rubella (MMR) vaccine to pregnant females; the possible side effects of the vaccine on fetal development are unknown at this time. If the vaccination of postpubertal females is

undertaken, pregnancy should be avoided for 3 months following the vaccination. Do not give varicella vaccinations to pregnant females.

If the patient is over the age of 35, the time required after immunization may not be in the patient's best interest. The patient may be counseled as to the risks of not accepting the rubella vaccination and offered the choice of not taking the time. If the patient chooses not to be immunized, the patient should sign a release form accepting risk.

Refer to the ICSI guideline Routine Prenatal Care, annotations "Rubella/Rubeola Status" and "Varicella Status" for a more complete text with references regarding rubella/rubeola and varicella status.

Algorithm II: Basic Infertility Work-up

10. Is Female Less Than 35 Years of Age?

    Fertility diminishes with age in women. This reduction is due to multiple factors such as decreased number and quality of oocytes, change in fertilizability and implantation of oocytes and embryos, and increased risk of chromosomal abnormalities resulting in spontaneous miscarriage. Fertility is rare after age 44 using one's own eggs.

    The age of 35 is not necessarily the age of transition in all women. Transition can occur in some women at an earlier age. There is no good test that measures relative fecundity or absolute fertility as a function of age.

    Evidence supporting this recommendation is of class: R

11. Obtain Day 3 Follicle Stimulating Hormone (FSH) and Estradiol

    Because of the reduced window of fertility potential in women over 35 years of age, the guideline work group recommends the most aggressive work-up for this age group. This might require earlier referral to an infertility specialist. This also may involve testing to determine ovarian reserve. Testing could be considered after age 35 and is encouraged after age 40. Any laboratory values of FSH and estradiol should be of question in laboratories that have not been standardized.

    Elevated FSH levels of day 3 of the menstrual cycle have been correlated to poor performance with assisted reproductive technology. The value of this test has not been well studied outside of these advanced procedures, but there is some intuitive value. Day 3 FSH values greater than 15 microIU/L probably reflect poor future reproductive potential. Day 3 FSH values less than 10 microIU/L represent normal follicular potential (especially if day 3 estradiol values are less than 40 pg/mL). Values between 10 to 15 microIU/L probably represent an effect of aging on fecundity. There is little value in repeat testing for these women and they should be referred to an infertility specialist.

    Evidence supporting this recommendation is of class: D

15. Are There Historical Factors Suggestive of Ovulatory Dysfunction Present?

Check the "historical character" of the menses (i.e., is there premenstrual syndrome [PMS] symptoms, or dysmenorrhea). Most women are ovulatory if they exhibit "classic" symptoms as the above and they have menstrual cycles occurring at 21 to 35-day intervals.

When menstrual cycle characteristics do not have historical characteristics of ovulation, then ovulation can be determined either by basal body temperature (BBT) or by serum progesterone levels.

Basal Body Temperature (BBT) for 3 Cycles

Instruct patients to take their temperatures using accurate or reliable BBT or digital thermometers before rising in the early morning. A "normal BBT" should be a biphasic curve with a temperature elevation of at least 0.4 degrees Fahrenheit for 12 to 15 days. Alternatively, over-the-counter urinary luteinizing hormone (LH) kits may be used to document the luteinizing hormone surge prior to ovulation. There is a cost issue with the use of LH kits (approximately $50 per kit). Patients should be instructed to mark down days when intercourse occurs so that the physician may note coital frequency. Irregular sleep habits will create more of a challenge in interpreting BBT charts.

Twenty percent of monophasic BBTs are still ovulatory. Check a day 21 serum progesterone (or 7 to 8 days post-ovulation) if BBT is monophasic but cycles are regular. A slow rise in a biphasic curve does not indicate a hormonal abnormality. One may also document ovulation by looking for an absence of a ferning pattern of the cervical mucus (i.e., progesterone effect) in a patient in her mid-luteal phase.

Evidence supporting this recommendation is of classes: B, C, R

Serum Progesterone Levels

Measure serum progesterone levels during the mid-luteal phase. More than one assay may need to be done to confirm the determination around the peak. The values suggest that progesterone greater than 6 is presumptive evidence of ovulation in the mid-luteal phase. Values of 2 to 3 ng/mL are borderline and need to be repeated.

A normal day 21 serum progesterone confirms normal corpus luteum production of progesterone, which is associated with normal ovulation. Use day 21 of a 28 day cycle, or check at 7 to 8 days post BBT shift if the cycle is longer or shorter. Day 21 progesterone levels greater than 3 ng/mL are indicative of ovulation. Values of greater than or equal to 10 ng/mL are suggestive of normal progesterone production. Progesterone secretion is pulsatile, and a single low level may not indicate a luteal defect.

Evidence supporting this conclusion is of class: R

Luteal Phase

A luteal phase of less than 12 days may correlate with a greater likelihood of a luteal phase defect. A luteal phase defect, however, can be present in patients who have a luteal phase of a normal length.

Evidence supporting this conclusion is of class: R

18. Obtain/Refer for Hysterosalpingogram (HSG)

Contraindications to HSG include:

- Possible pregnancy
- Abnormal uterine bleeding, abnormal last menstrual period (rule out pregnancy)
- Acute pelvic inflammatory disease
- Recent curettage or active genital tract infection
- Nontoxic goiter
- Endemic iodine deficiency
- Present metformin use

Evidence supporting this recommendation is of classes: M, R

Although the risks for the procedure related to infection is less than 1%, prophylactic antibiotics should be considered when there is a history of pelvic inflammatory disease but no pelvic tenderness on exam and/or there is a history of septic abortion or endometritis.

Evidence supporting this recommendation is of classes: C, D, R

Nonionic Dye or Benadryl w/glucocorticoids are recommended for prophylaxis in cases with a known sensitivity to iodine exists.

In situations of previous iodine anaphylaxis it would be more acceptable to perform hysteroscopy and laparoscopy in lieu of HSG.

Evidence supporting this recommendation is of class: R

Pre-procedure analgesia, while optional, may be prescribed using over-the-counter nonsteroidal anti-inflammatory medications or intramuscular injection of a narcotic (such as meperidine) or of a nonsteroidal anti-inflammatory (such as ketorolac).

Evidence supporting this recommendation is of class: R

20. Consider Laparoscopy or Empiric Treatment of Infertility

A laparoscopy is often the final diagnostic procedure in an infertility evaluation. More recently a debate has emerged concerning the cost/benefit value of laparoscopy in patients with a normal hysterosalpingogram (HSG). Some authors have suggested deleting the laparoscopy in patients with a

normal hysterosalpingogram, negative chlamydia antibody titer testing, and normal pelvic ultrasound because of low prevalence of significant pelvic abnormalities that would affect future treatment decisions. Many of these arguments for and against laparoscopy depend on the controversial value of surgical treatment of Stage 1 and 2 endometriosis in improving conception rates. Without these factors, empiric therapy with ovarian hyperstimulation and interuterine inseminations might be considered as an approach.

Evidence supporting this recommendation is of classes: D, R

22. Are There Suggestive Factors of Androgenic Ovulatory Dysfunction?

Androgenicity is clinically variable. Even mild degrees of androgenicity should be evaluated. The most sensitive marker for increased androgen production is hirsutism. Hirsutism may be influenced by ethnicity; Caucasians are more hirsute than Blacks, who are in turn more hirsute than Asians. Other symptoms of androgenic hyperfunction include acne, menstrual irregularities, increased libido, clitoromegaly, and finally masculinization. Sexual hair (hair that responds to sex steroids) is located on the face, lower abdomen (male escutcheon), anterior thighs, chest, breasts, pubic and axillary areas.

Evidence supporting this recommendation is of class: R

23. Hormonal Workup for an Androgenic and/or Centripetally Obese Patient

Obtain Values For:

- Thyroid stimulating hormone (TSH)
- Follicle stimulating hormone and luteinizing hormone (FSH) and luteinizing hormone (LH)
- Total serum testosterone
- Dehydroepiandrosterone sulfate (DHEA-S)
- Prolactin
- 17-hydroxyprogesterone levels:

  When the a.m. 17-hydroxyprogesterone levels obtained during the presumed follicular phase are abnormal, refer to an endocrinologist.

- Fasting and 2-hour post 75 gm blood glucose values

  Women with polycystic ovarian syndrome (defined as symptoms of an ovulatory disorder and hirsutism) are insulin resistant and are at high risk for glucose intolerance. The American Diabetes Association diagnostic criteria for diabetes are probably inadequate for screening patients with polycystic ovarian syndrome. A higher percentage of patients with diabetes will be defined using World Health Organization (WHO) criteria:

  - Fasting blood sugar greater than or equal to 125 mg/dL OR

- 2-hour post 75 gram glucose greater than or equal to 200 mg/dL
- Impaired glucose fasting tolerance glucose is 100-125 mg/dL OR
- Impaired glucose tolerance 2-hour post 75 gram glucose is 140-199 ml/dL

- Consider a fasting lipid panel: total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides.

  Metabolic syndrome is commonly seen in women with polycystic ovarian syndrome (PCOS).

  Insulin resistance is present in 50 to 70% of women with PCOS. Lifestyle changes including diet modification and exercise improves both insulin sensitivity and ovulation rates in obese PCOS patients even independent of weight loss. Weight loss is clearly beneficial. In women with PCOS, the use of insulin-sensitizing drugs increases spontaneous ovulation, ovulation with clomiphene citrate, and pregnancy rates. Controversy exists over determining which women have insulin resistance and whether these drugs should be used alone or in conjunction with clomiphene citrate. Use of the fasting glucose-to-insulin ratio has been suggested to select women who are candidates for insulin sensitizing drugs. A ratio of less than 4.5 may be indicative of insulin resistance in Caucasian women. Unfortunately there is no evidence that this ratio is predictive of response (ovulation and pregnancy rates) to insulin-sensitizing drugs. Others suggest the use of insulin-sensitizing drugs for all women with PCOS regardless of lab test results, especially in those unresponsive to clomiphene citrate.

Evidence supporting this recommendation is of classes: C, R

24. Obtain Thyroid Stimulating Hormone (TSH), Prolactin, Follicle Stimulating Hormone (FSH), and Estradiol

    Short luteal phases are a potential precursor to premature ovarian failure. The thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH), prolactin, and estradiol tests assist in determining whether or not a non-biphasic temperature chart might be ovulatory in spite of a lack of temperature changes. If the patient is cycling, testing should be done on day 3. If the patient is proven to be hypoestrogenic, calcium and vitamin D supplements should be recommended. Estrogen supplementation should also be recommended if the patient is going to defer child bearing.

30. Semen Analysis Normal?

    Semen analysis is routinely used to determine the presence of male factor infertility. However, the values for normal seminal parameters are not well defined. While semen analysis lacks specificity, there is, unfortunately, not another screening tool which would be better. The WHO criteria for semen analysis outline the minimal standards for sperm measurements but do not necessarily identify men with male factor infertility. Values are given for sperm concentration, motility, and morphology to classify men as subfertile,

of indeterminate fertility, and fertile. For this reason the following guidelines should be used in evaluating a semen analysis for possible male factor infertility.

Subfertile (previously classified as infertile)

- Sperm concentration - less than 20.0 X 10^6 sperm/mL
- Sperm motility - less than 50%
- Sperm morphology (WHO) - less than 30% normal forms

Indeterminate range (possible male factor infertility)

- Sperm concentration - 20.0 - 40.0 X 10^6 sperm/mL
- Sperm motility – less than 50%
- Sperm morphology (WHO) - less than 30% normal forms

Fertile (no evidence of male factor infertility)

- Sperm concentration - greater than 40 X 10^6 sperm/mL
- Sperm motility - greater than 50%
- Sperm morphology (WHO) - greater than 30% normal forms

Males who have any seminal parameters that fall within the range of subfertile or indeterminate should have a repeat semen analysis. Men with persistent values in the subfertile or indeterminate range should be referred to a male infertility specialist.

Evidence supporting this recommendation is of class: C

Post-Coital Testing

The infertility guideline work group agrees that the post-coital test should be deleted from the basic infertility evaluation. This conclusion is based on:

1. The limited correlation to fertility
2. The confusion about standardized normal values
3. The controversies about follow-up treatment
4. The tendency of abnormal tests to create further testing without an apparent significant effect on the pregnancy rate
5. The increasing use of empiric superovulation and intrauterine insemination treatment in infertility makes the post-coital test superfluous.

Evidence supporting this recommendation is of classes: A, B, C, D

Algorithm III: Evaluation of Ovulation Dysfunction

35. Conduct Progesterone Challenge Test

The progesterone challenge test is done to confirm the presence of an estrogen-primed endometrium. The usual dosage is Prometrium 400 mg every p.m. for 10 days.

Evidence supporting this recommendation is of class: R

36. Withdrawal Bleeding?

A withdrawal bleed indicates the presence of a reactive endometrium that was adequately formed by endogenous estrogen.

Consult a reproductive endocrinologist.

Evidence supporting this recommendation is of class: C

37. Consult to Infertility Specialist for Gonadotropin Therapy or Gonadotropin Releasing Hormone Pump Therapy

The patient demonstrates a lack of withdrawal bleeding and most likely is severely hypoestrogenic with hypothalamic amenorrhea. Consider, however, rare cases of Asherman's Syndrome (ablation of endometrial cavity) or anatomic outflow tract obstruction problem. The patient will need a referral to an infertility specialist for evaluation and appropriate treatment such as gonadotropins or the gonadotropin releasing hormone (GnRH) pump.

Evidence supporting this recommendation is of class: D

39. Consult a Gynecologist Familiar with Reproductive Endocrinology to Evaluate and Treat for Specific Problem

Thyroid Dysfunction

Evaluate and treat thyroid dysfunction as indicated by an abnormal sensitive TSH. A suppressed TSH (less than 0.35 microIU/mL) is found in hyperthyroid patients or in patients on suppressive thyroid medications, or possibly in patients with hypothalamic pituitary disease. Conversely, a high sensitive TSH (greater than 5.0 microIU/mL) is consistent with primary hypothyroidism, and thyroid hormone replacement should restore normal menses, especially when the TSH is greater than 10 microIU/mL.

Evidence supporting this recommendation is of class: D

Elevated Prolactin

An elevated prolactin (greater than 25 ng/mL, or use your own reference lab's norms) can cause oligo/anovulation as well as a luteal phase inadequacy. Check for galactorrhea, which is seen in 1/3 of hyperprolactinemic women. Ideally, obtain the serum prolactin as a fasting AM level (diurnal variation exists). Be aware that other factors such as increased stress, time in the menstrual cycle, etc., may influence the result. Also rule out the use of certain drugs that may cause an elevated prolactin (phenothiazines,

amphetamines, reserpine, opiates, diazepam, methyldopa, and tricyclic antidepressants). Prolactin elevations above laboratory threshold levels require either a computed tomography (CT) scan or a magnetic resonance imaging (MRI) of the head to rule out a pituitary adenoma. Pituitary prolactinomas may be suppressed with dopamine agonists.

Evidence supporting this recommendation is of classes: C, D

Elevated DHEA-S

An endocrine consult should be obtained when the DHEA-S is elevated. Greater than 6 months of glucocorticoid use is associated with mild elevations of DHEA-S and can be treated with dexamethasone (0.5 mg HS daily) during ovulation induction therapy cycles if one does not exceed one year of clomiphene use. The patient should be counseled about glucocorticoid side effects such as aseptic necrosis of the femoral head and osteoporosis. If DHEA-S is significantly elevated (greater than 7000 ng/mL or approximately 2x normal), suspect an adrenal tumor or congenital adrenal hyperplasia.

Evidence supporting this recommendation is of class: A

Elevated Total Serum Testosterone

Elevated total serum testosterone is most commonly seen in functional ovarian disorders like polycystic ovarian syndrome. Consider both adrenal and primarily ovarian sources if you find sole elevations of serum testosterone. Highly elevated levels (greater than 200 ng/mL or use your own reference lab's norms) may be associated with androgen-producing ovarian tumors. An endocrine consult should be considered.

If FSH is significantly elevated, rule out premature ovarian failure and refer to an infertility specialist.

Evidence supporting this recommendation is of class: D

40. Begin Using Clomiphene

Clomiphene citrate therapy is usually started at a dose of 50 mg daily for 5 days starting at day 3 to 5 of each cycle. Occasionally, 25 mg of clomiphene is appropriate for a thin, hypoandrogenic patient. Failure to ovulate at the 50-mg dose requires increasing the dose by 50-mg increments up to a maximum of 150 mg per day. Doses of clomiphene greater than 150 mg are rarely beneficial, but may be required in some cases such as in extreme obesity. Discuss the risks of multiple pregnancy and ovarian cysts, as well as theoretical concerns regarding ovarian malignancies associated with clomiphene. Reassess the infertility therapy plan after 3 optimal cycles if no conception occurs. Documentation of ovulatory response to clomiphene should be undertaken using basal body temperature charts and/or mid-luteal phase progesterone (6 mg/mL) levels. Once adequate ovulation cycles from charts have been achieved, going to higher doses of clomiphene does not appear to have value or a beneficial effect and may be counterproductive. If

the patient has not become pregnant after 3 cycles, the patient should be reassessed and considered for referral to a reproductive endocrinologist. Metformin alone or in conjunction with clomid has been found to be effective in inducing ovulation in hyperandrogenic women with insulin resistance at doses of 500 mg three times a day or 850 mg twice a day.

Evidence supporting this recommendation is of classes: D, R

41. Consider Luteal Phase Evaluation, Hysterosalpingography (HSG), and Optional Luteal Phase Evaluation

There is present debate as to the necessity as well as timing of hysterosalpingography (HSG) in patients with apparent ovulatory factor infertility. Most infertility specialists nevertheless recommend HSG either prior to or during the first few cycles of clomiphene citrate ovulation induction to rule out a concurrent tubal factor.

Clomiphene citrate may have potentially adverse effects on cervical mucus and endometrial morphology. For these reasons, some have advocated evaluation of the luteal phase (late luteal phase endometrial biopsy) and cervical mucus during the initial cycles of clomiphene citrate therapy. Both of these tests, however, must be timed properly and are subject to variability of interpretation. In addition, there have been no well-designed prospective studies demonstrating the predictive value of endometrial biopsy or cervical mucus test on pregnancy outcome while on clomiphene citrate. Therapeutic options (use of progesterone vaginal suppositories, use of intrauterine inseminations, or altering the dose of clomiphene citrate, etc.) in the setting of an abnormal luteal phase endometrial biopsy or post-coital test on clomiphene citrate have a physiologic basis although remain unproven.

Similarly, certain investigators have also recently advocated the use of transvaginal ultrasonography in the monitoring of endometrial response in patients on clomiphene citrate therapy. It has been suggested that the anti-estrogen effects of clomiphene citrate on the endometrium may be inferred by reduced endometrial thickness measurements. At this time, the clinical utility of transvaginal ultrasonography in monitoring clomiphene citrate response remains controversial. Several investigators, however, have demonstrated lower pregnancy rates in the presence of a decreased endometrial thickness or in the absence of a trilaminar endometrial pattern. These findings have resulted in some investigators advocating: the delay of human chorionic gonadotropin (HCG) administration, the use of estrogen supplementation, or change in ovulation-inducing medications when these findings are noted and pregnancy is not occurring.

Evidence supporting this recommendation is of classes: C, M

44. Continue Treating with 3 to 6 Cycles Clomiphene

One should reassess the infertility therapy plan if there is no success after 3 optimal cycles. Additional cycles, up to a total of 6 cycles, can be considered if other factors are identified and treated. If there is no success after 6 optimal cycles, refer to Reproductive Endocrinologist.

Evidence supporting this recommendation is of class: D

46. Consider Laparoscopy and/or Alternative Ovulation Induction

Laparoscopy is often the final diagnostic procedure in an infertility evaluation. It has value to follow up on hysterosalpingography abnormalities and to evaluate problems the hysterosalpingogram cannot evaluate, such as endometriosis and pelvic adhesions. Therapeutic correction of noted abnormalities is also possible at the time of surgery. Alternative ovulation induction with gonadotropins regimen could be used in women with clomiphene resistant polycystic ovarian syndrome. Ovarian drilling is as effective as gonadotropin therapy.

Evidence supporting this recommendation is of classes: M, R

Algorithm IV: Abnormal Hysterosalpingogram

48. Abnormal Hysterosalpingogram (HSG)

Hysterosalpingography entails injection of radiopaque dye through the uterus with fluoroscopic visualization of the uterine cavity and tubal lumen. The resulting hysterosalpingogram (HSG) is useful in detecting abnormalities such as uterine anomalies and fallopian tube occlusion in women with histories of repetitive spontaneous abortion and infertility.

Evidence supporting this recommendation is of class: R

49. Provide Couple With Education Materials

The couple should be provided with appropriate educational materials.

56. Repeat HSG or Laparoscopy, Each With Tubal Cannulation Capability

Reevaluation should be done in a facility in which a tubal cannulation can be immediately attempted should tubal occlusion be reconfirmed. If surgical treatment is undertaken, it should be performed by a surgeon with the capability of doing not only tubal cannulation, but also any necessary surgical anastomosis if cannulation fails. When tubal cannulation fails, proximal tubal occlusion may be treated by microsurgical tubocornual reanastomosis (TCA) if a significant length of otherwise normal fallopian tube remains. Ideal candidates for TCA generally have a normal pelvis, total tubal lengths of greater than 6 cm, ampullary lengths of greater than 3 cm, and a normal fimbria. TCA under optimal conditions may be associated with a 50 to 70% pregnancy rate.

Proximal tubal occlusion should be confirmed by either repeat laparoscopy or hysterosalpingogram with tubal cannulation possibilities. If confirmed, a cannulation is always attempted first before TCA.

Fluoroscopic or hysteroscopic tubal cannulation is a much less invasive procedure than TCA, and is associated with similar pregnancy rates. Tubal

cannulation should always be attempted first before TCA is considered unless isolated severe proximal tubal disease precludes the likelihood of successful cannulation.

Evidence supporting these recommendations is of classes: C, D, R

57. Continue Infertility Evaluation or Consider Surgical Treatment

If surgical treatment is undertaken, it should be undertaken by a surgeon with the capabilities of doing not only tubal cannulation but also any necessary surgical anastomosis if the cannulation is a failure.

61. Assess Preoperative Prognostic Factors, Counsel Patient

Several hysterosalpingogram abnormalities have been found to be associated with poor outcome following corrective surgery. These include proximal tubal diverticula indicated salpingitis, isthmica nodosum, hydrosalpinx greater than 3 cm in diameter, and loss of rugal folds. The presence of any of these bad prognostic findings indicates a decreased pregnancy rate following salpingostomy, and would be less than expected from a single cycle of invitro fertilization. Counsel the patient about poor outcomes related to these abnormalities and about in vitro fertilization (IVF) as an option. IVF would have more success than surgery for any of these prognostic factors. IVF can be offered as an alternative to procedures for abdominal reanastomosis.

63. If Hydrosalpinx is Present: IVF with Laparoscopic Salpingectomy or Tubal Ligation

Recent evidence indicates that patients who have a hydrosalpinx as a consequence of pelvic inflammatory disease that communicates with the uterine cavity experience a decreased pregnancy rate following in-vitro fertilization and embryo transfer. Patients who have a communicating hydrosalpinx should be considered as candidates for a laparoscopic partial or total salpingectomy to either remove or isolate the hydrosalpinx.

Evidence supporting these recommendations is of classes: A, C

Algorithm V: Male infertility - Primary Care Work-Up

74. Initial Workup
    A. History

The history should include the following:

- Marital history including previous fertility of partners and frequency of intercourse
- General health including previous illnesses and recent febrile illness (in past 2-6 months)
- History of gynecomastia
- Shaving frequency
- Family history of infertility

- Chemical/radiation exposure including: smoking history, medications, past chemotherapy, industrial exposure (especially to organic solvents and heavy metals)
- Genital surgery: hernia repair, hydrocelectomy, retroperitoneal surgery, cystoscopy
- Genital inflammation: urethritis, epididymitis, mumps orchitis, prostatitis
- Genital trauma: especially if associated with disability or scrotal ecchymosis
- History of erectile dysfunction: inability to provide a sample

B. Physical Examination

The physical examination should be performed in the upright position.

Major factors associated with male infertility include:

- Scrotal contents:
  - Testes - size and consistency
  - Epididymis - size, consistency, spermatoceles
  - Vas deferens - presence, size
  - Varicocele - if palpable, size, medium or large
  - Prostate gland - size and consistency

Minor factors which may be associated with male infertility include:

- Obesity
- Breast hair distribution
- Penile abnormalities

C. Two Semen Analyses

Laboratory Qualifications for Semen Analysis

- High complexity lab meeting Clinical Laboratory Improvement Amendments 88 (CLIA) accreditation standards and using World Health Organization criteria.
- Stain for round cell differentiation

The patient should be instructed on the following specifications for an optimal sample:

- Collect ejaculate after abstinence for 2 to 5 days by masturbation into sterile container supplied by medical center. Do not use lubricants or saliva. If any portion of ejaculate is lost, note this. Do not use condoms.
- The sample should be delivered to the lab within 30 minutes (ideally collected on site) of collection.
- The sample should be kept at body temperature (55 to 99 degrees F).

Before accepting a semen sample for analysis, the laboratory should verify that the sample meets the quality control criteria noted in the patient education section above.

A complete semen analysis also provides information on other factors in the semen. If any of the components of the semen analysis falls outside of normal, consider the results abnormal.

Components	Normal values
Motility - forward progression	Local standards
pH	7.2 to 8.0
Round cell differentiation	White blood cells (wbc) less than 1 million/mL
White cell versus germinal	Germinal less than 4 million/mL
Motile sperm per ejaculate	Greater than 20 million
Agglutination	None to minimal
Viscosity	Normal
Volume	1.5 to 5 mL

75. Evidence supporting this recommendation is of class: R

76. Repeat Semen Analysis in Four Months if No Pregnancy

When the initial semen analysis is normal, a period of observation is warranted. The repeat semen analysis is delayed for four months in order to coincide with the spermatogenic cycle.

Evidence supporting this recommendation is of class: R

79. Gonadotoxin Exposure?

Gonadotoxins are chemicals, drugs, or other substances that have a toxic or suppressive effect on sperm production, motility, or morphology. Their effect is usually reversible if exposure is discontinued. Gonadotoxins may act indirectly via the hypothalamic-pituitary-gonadal axis, directly on the testicle, or even at the post-testicular level. (Refer to the original guideline document for more information.)

Evidence supporting this recommendation is of class: C

82. Refer to Specialist for Male Infertility

When the patient is referred to a male infertility specialist for further evaluation, obtain the following tests in advance of the appointment:

- FSH
- Testosterone

Obtain morning FSH and testosterone levels. The most accurate time for obtaining hormone levels in males is in the morning. Afternoon blood draws may lead to inaccurate measurements of FSH and testosterone.

If serum testosterone is low, or if the patient has symptoms of decreased libido and/or decreased potency, obtain a repeat serum testosterone, a free testosterone level, a luteinizing hormone level, and a prolactin level.

Evidence supporting this recommendation is of class: R

84. Symptoms of Infection?

The majority of infertility patients with urogenital infection will present with symptoms. Pertinent history should be taken from both partners, as many urogenital infections are sexually transmissible and may not be symptomatic. Symptoms of infection may include urethral discharge, dysuria, meatal soreness, frequent voiding, poor urinary stream, testicular/suprapubic/perineal pain, scrotal swelling, hematospermia, pain with ejaculation. Signs of infection include greater than 2 to 3 white blood cells per high-power field (wbc/hpf) centrifuged urine, greater than 5 to 10 white blood cells per high-power field expressed prostatic secretion, greater than 1 million white blood cells/mL semen, meatal swelling/erythema, urethral discharge, swelling/tenderness epididymis, swelling/tenderness prostate.

A semen stain for white blood cells should be documented.

Evidence supporting this recommendation is of class: R

85. Consider Empiric Treatment

Empiric treatment with antibiotics and anti-inflammatories may be reasonable. Use doxycycline 100 mg twice a day for 7 to 10 days or an appropriate fluoroquinolone antibiotic for 7 to 10 days. A 7 to 10 day course of doxycycline is recommended for both partners.

Evidence supporting this recommendation is of classes: A, C, R

87. Refer to Male Infertility Specialist

Proper evaluation and treatment of male infertility require an adequate fund of knowledge as well as clinical experience with the various causes and treatment of male infertility. General urologists typically have an understanding of male infertility but do not necessarily have extensive experience in the evaluation and treatment of male infertility. The ideal male

infertility specialist will have completed a urology residency and have fellowship training in male infertility. A general urologist who dedicates at least 30% of his/her clinical practice to the evaluation and treatment of male infertility could be used as a substitute if a fellowship-trained male infertility specialist is not easily accessible.

88. Repeat Semen Analysis in One Month

    If the first semen analysis is abnormal, a second semen analysis should be ordered to be performed in one month. Careful instructions regarding abstinence, collection, and transportation of the specimen should be repeated.

    Evidence supporting this recommendation is of class: R

Definitions:

Classes of Research Reports:

A. Primary Reports of New Data Collection:

   Class A:

   - Randomized, controlled trial

   Class B:

   - Cohort study

   Class C:

   - Nonrandomized trial with concurrent or historical controls
   - Case-control study (except as above)
   - Study of sensitivity and specificity of a diagnostic test
   - Population-based descriptive study

   Class D:

   - Cross-sectional study
   - Case series
   - Case reports

B. Reports that Synthesize or Reflect upon Collections of Primary Reports

   Class M:

   - Meta-analysis
   - Systematic review
   - Decision analysis
   - Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

CLINICAL ALGORITHM(S)

Detailed and annotated clinical algorithms are provided for:

- Initial Screening
- Basic Infertility Work-Up
- Evaluation of Ovulation Dysfunction
- Abnormal Hysterosalpingogram
- Male Infertility - Primary Care Work-Up

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The guideline contains an annotated bibliography and discussion of the evidence supporting each recommendation. The type of supporting evidence is identified and classified for selected recommendations (see "Major Recommendations"). The workgroup acknowledges that there is a lack of Class A (randomized controlled trial) and Class B (cohort study) evidence for diagnostic and therapeutic trials pertaining to infertility.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Improve fertility rates
- Improve the management of infertility

POTENTIAL HARMS

Clomiphene Citrate Therapy

Clomiphene citrate may have potentially adverse effects on cervical mucus and endometrial morphology. The use of clomiphene has been associated with risks of multiple pregnancy, ovarian cysts, and theoretical concerns regarding ovarian malignancies.

Complications of Hysterosalpingography (HSG)

The overall incidence of infection with HSG is probably less than 1%, although with high risk populations, serious infections can occur in 3% of cases.

Allergic Reaction to Iodine Contrast Dye with Hysterosalpingography

Allergic reactions consist of urticaria and syncope. Nonionic Dye or Benadryl w/ glucocorticoids are recommended for prophylaxis in cases with a known sensitivity to iodine.

CONTRAINDICATIONS

CONTRAINDICATIONS

Contraindications to Hysterosalpingography (HSG)

- Possible pregnancy
- Abnormal uterine bleeding, abnormal last menstrual cycle (rule out pregnancy)
- Acute pelvic inflammatory disease
- Recent curettage or active genital tract infection
- Nontoxic goiter
- Endemic iodine deficiency
- Present metformin use

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- These clinical guidelines are designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and are not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem.
- This medical guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients are urged to consult a health care professional regarding their own situation and any specific medical questions they may have.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Once a guideline is approved for general implementation, a medical group can choose to concentrate on the implementation of that guideline. When four or more groups choose the same guideline to implement and they wish to collaborate with others, they may form an action group.

In the action group, each medical group sets specific goals they plan to achieve in improving patient care based on the particular guideline(s). Each medical group shares its experiences and supporting measurement results within the action

group. This sharing facilitates a collaborative learning environment. Action group learnings are also documented and shared with interested medical groups within the collaborative.

Currently, action groups may focus on one guideline or a set of guidelines such as hypertension, lipid treatment, and tobacco cessation.

Detailed measurement strategies are presented in the original guideline document to help close the gap between clinical practice and the guideline recommendations. Summaries of the measures are provided in the National Quality Measures Clearinghouse (NQMC).

IMPLEMENTATION TOOLS

Clinical Algorithm
Pocket Guide/Reference Cards
Quality Measures

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

RELATED NQMC MEASURES

- Diagnosis and management of basic infertility: percentage of women treated for infertility where both partners are assessed during the basic infertility work-up.
- Diagnosis and management of basic infertility: percentage of women with either laparoscopies or tubal surgery with recommended prior tests.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Diagnosis and management of basic infertility. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2004 Jul. 47 p. [85 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1996 Feb (revised 2004 Jul)

GUIDELINE DEVELOPER(S)

Institute for Clinical Systems Improvement - Private Nonprofit Organization

GUIDELINE DEVELOPER COMMENT

Organizations participating in the Institute for Clinical Systems Improvement (ICSI): Affiliated Community Medical Centers, Allina Medical Clinic, Altru Health System, Aspen Medical Group, Avera Health, CentraCare, Columbia Park Medical Group, Community-University Health Care Center, Dakota Clinic, ENT Specialty Care, Fairview Health Services, Family HealthServices Minnesota, Family Practice Medical Center, Gateway Family Health Clinic, Gillette Children's Specialty Healthcare, Grand Itasca Clinic and Hospital, HealthEast Care System, HealthPartners Central Minnesota Clinics, HealthPartners Medical Group and Clinics, Hutchinson Area Health Care, Hutchinson Medical Center, Lakeview Clinic, Mayo Clinic, Mercy Hospital and Health Care Center, MeritCare, Mille Lacs Health System, Minnesota Gastroenterology, Montevideo Clinic, North Clinic, North Memorial Care System, North Suburban Family Physicians, Northwest Family Physicians, Olmsted Medical Center, Park Nicollet Health Services, Pilot City Health Center, Quello Clinic, Ridgeview Medical Center, River Falls Medical Clinic, Saint Mary's/Duluth Clinic Health System, St. Paul Heart Clinic, Sioux Valley Hospitals and Health System, Southside Community Health Services, Stillwater Medical Group, SuperiorHealth Medical Group, University of Minnesota Physicians, Winona Clinic, Ltd., Winona Health

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GUIDELINE COMMITTEE

Ob/Gyn Steering Committee

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

In the interest of full disclosure, Institute for Clinical Systems Improvement (ICSI) has adopted the policy of revealing relationships work group members have with companies that sell products or services that are relevant to this guideline topic. The reader should not assume that these financial interests will have an adverse impact on the content of the guideline, but they are noted here to fully inform readers. Readers of the guideline may assume that only work group members listed below have potential conflicts of interest to disclose.

No work group members have potential conflicts of interest to disclose.

ICSI's conflict of interest policy and procedures are available for review on ICSI's website at www.icsi.org.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Institute for Clinical Systems Improvement (ICSI). Diagnosis and management of infertility. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2003 Apr. 54 p.

GUIDELINE AVAILABILITY

Electronic copies of the revised guideline: Available from the Institute for Clinical Systems Improvement (ICSI) Web site.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- ICSI pocket guidelines. April 2004 edition. Bloomington (MN): Institute for Clinical Systems Improvement, 2004. 404 p.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

PATIENT RESOURCES

None available

NGC STATUS

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